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# Inside This Issue

STATE-OF-THE-ART-PAPER

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**LAA Occlusion** 291

*David R. Holmes, Jr, Dhanunjaya R. Lakkireddy, Richard P. Whitlock, Ron Waksman, Michael J. Mack*

Despite the use of oral anticoagulants, stroke prevention in patients with atrial fibrillation remains challenging. Furthermore, a significant number of patients are not candidates for anticoagulation therapy, leaving them at significant risk for stroke. In this state-of-the-art paper, Holmes and colleagues review the current status of both surgical and catheter-based left atrial appendage (LAA) closure devices. Results of trials comparing LAA closure devices to anticoagulation therapy are reviewed. Additionally, the challenges faced in obtaining regulatory approval for these devices are discussed.

CLINICAL RESEARCH

INTERVENTIONAL CARDIOLOGY

**Durable Versus Bioabsorbable Polymer DES** 299

*Tullio Palmerini, Giuseppe Biondi-Zoccai, Diego Della Riva, Andrea Mariani, Manel Sabaté, Pieter C. Smits, Christoph Kaiser, Fabrizio D'Ascenzo, Giacomo Frati, Massimo Mancone, Philippe Genereux, Gregg W. Stone*

The authors investigate the relative safety and efficacy of bioabsorbable polymer (BP)–based biolimus-eluting stents (BES) versus durable-polymer drug-eluting stents (DES) and bare-metal stents (BMS) using network meta-analysis. Data from 89 trials including 85,490 patients were analyzed. Results revealed that BP-BES were associated with superior clinical outcomes compared with BMS and first-generation DES, similar rates of cardiac death/myocardial infarction (MI), MI, and target vessel revascularization compared with second-generation BP-BES, but higher rates of definite stent thrombosis than Cobalt-chromium everolimus-eluting stents.

*Editorial Comment: John A. Bittl, p. 308*

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CARDIAC SURGERY

## ARAS and Cardiac Surgery 310

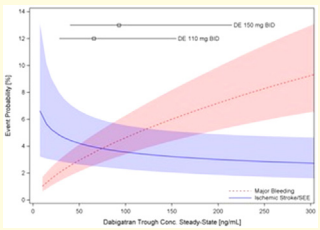
*Femi Philip, Heather L. Gornik, Jeevanantham Rajeswaran, Eugene H. Blackstone, Mehdi H. Shishehbor*

The impact of atherosclerotic renal artery stenosis (ARAS) on acute kidney injury (AKI) after open-heart surgery (OHS) is unknown. The aim of this study was to further investigate the significance of this association. A total of 714 patients (mean age of 67 ± 12 years) undergoing OHS also had renal duplex ultrasound performed. The average glomerular filtration rate (GFR) was 52 ± 25.9 ml/min/1.73 $m^2$, and 206 (29%) subjects had ARAS. Adjusted models showed a nonsignificant trend between ARAS and reduction in GFR post-surgery. ARAS was also not associated with a need for renal replacement therapy, longer length of stay (LOS), or mortality; however, a lower pre-operative GFR was a strong predictor of long-term mortality independent of ARAS. Philip and colleagues conclude that ARAS does not appear to be associated with post-operative changes in GFR, need for hemodialysis, longer LOS, or mortality in patients undergoing OHS.

*Editorial Comment: Giuseppe Biondi-Zoccai, Massimo Mancone, Giacomo Frati, p. 317*

ANTITHROMBOTIC THERAPY

## Dabigatran Exposure Response in AF Patients 321




*Paul A. Reilly, Thorsten Lehr, Sebastian Haertter, Stuart J. Connolly, Salim Yusuf, John W. Eikelboom, Michael D. Ezekowitz, Gerhard Nehmiz, Susan Wang, Lars Wallentin, on behalf of the RE-LY Investigators*

This study analyzed the impact of dabigatran plasma concentration, patient demographics, and aspirin (ASA) use on the frequency of ischemic strokes/systemic emboli and major bleeds in patients with atrial fibrillation. Plasma concentrations of dabigatran were determined in 9,183 patients (from the RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy] trial) treated with dabigatran etexilate 110 or 150 mg twice daily. A total of 112 ischemic stroke/systemic emboli (1.3%) and 323 major bleeds (3.8%) were recorded. Dabigatran levels were dependent on renal function, age, weight, and female sex. A multiple logistic regression model (c-statistic: 0.657) showed that the risk of ischemic events was inversely related to trough dabigatran concentration, with age and previous stroke as significant covariates. Major bleeding risk increased with dabigatran exposure, with age, aspirin use, and diabetes as significant covariates. Reilly and colleagues conclude that ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations, with age as the most important covariate.

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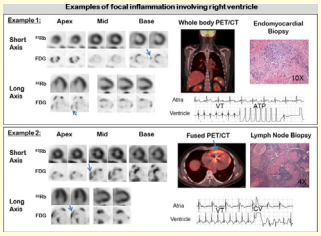



CARDIAC IMAGING

## Use of PET in Cardiac Sarcoidosis 329

*Ron Blankstein, Michael Osborne, Masanao Naya, Alfonso Waller, Chun K. Kim, Venkatesh L. Murthy, Pedram Kazemian, Raymond Y. Kwong, Michifumi Tokuda, Hicham Skali, Robert Padera, Jon Hainer, William G. Stevenson, Sharmila Dorbala, Marcelo F. Di Carli*

The investigators of this study attempted to correlate image findings on positron emission tomography (PET) to adverse cardiac events in patients referred for evaluation of known or suspected cardiac sarcoidosis (CS). A total of 118 consecutive patients, with no history of coronary artery disease, who were referred for PET using $^{18}$F-fluorodeoxyglucose (FDG) (to assess for inflammation) and $^{82}$Rubidium (to evaluate for perfusion defects [PD]) were followed. Among the 118 patients (age 52 ± 11 years; 57% male, mean ejection fraction 47 ± 16%), 47 (40%) had normal and 71 (60%) abnormal cardiac PET findings. Over a median follow-up of 1.5 years, there were 31 (26%) adverse events (27 ventricular tachycardia [VT] and 8 deaths). Cardiac PET findings were predictive of adverse events, with the presence of both a PD and abnormal FDG (29% of patients) being associated with a hazard ratio of 3.9, which was significant even after adjusting for left ventricular ejection fraction and clinical criteria. Blankstein and colleagues conclude that the presence of focal PD and FDG uptake on cardiac PET identifies patients at high risk of death or VT.

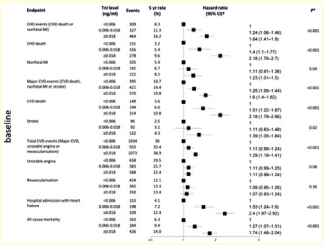
CARDIAC IMAGING

## Prognostic Impact of DSE in Kawasaki Disease 337

*Nobutaka Noto, Hiroshi Kamiyama, Kensuke Karasawa, Mamoru Ayusawa, Naokata Sumitomo, Tomoo Okada, Shori Takahashi*

Noto and colleagues of this study sought to determine the prognostic value of dobutamine stress echocardiography (DSE) for predicting cardiac events in adolescent Kawasaki disease (KD) patients with coronary artery lesions (CALS). A total of 58 KD patients, including 36 patients with CALS documented by quantitative coronary angiography and 22 patients with normal coronary artery documented by echocardiography, who underwent DSE were reviewed at initial testing (mean age 13.6 years) and at 15-year follow-up. During a mean follow-up of 14.7 years, there were 16 patients with major adverse cardiac events (MACE) (acute myocardial infarction: n = 1, old myocardial infarction: n = 7, coronary artery bypass grafting: n = 4, percutaneous coronary intervention: n = 4). Significant coronary artery disease (CAD) (>70% coronary stenosis) was detected in 31.0% patients at initial testing and 42.1% at follow-up. Five (85%) of 6 patients with false-positive DSE (wall motion score index ≥1.25) at initial testing, who all had giant aneurysm without CAD, developed CAD with MACE during follow-up. Cox regression analysis showed the grade of peak wall motion score index at initial testing to be the only independent predictor of MACE. The authors conclude that DSE provides independent prognostic information for up to 15 years in adolescent KD survivors.

(*continued on page A-29*)



BIOMARKERS

## 1-Year Change in Sensitive Troponin I and Coronary Events 345

*Harvey D. White, Andrew Tonkin, John Simes, Ralph Stewart, Kristy Mann, Peter Thompson, David Colquhoun, Malcolm West, Paul Nestel, David Sullivan, Anthony C. Keech, David Hunt, Stefan Blankenberg, for the LIPID Study Investigators*

The objective of this study was to assess whether baseline and changes in the contemporary sensitive (Siemens Ultra, Erlangen, Germany) troponin I (TnI) predict coronary heart disease (CHD) and myocardial infarction (MI), and the effect of pravastatin on TnI levels and relationship with outcomes. A total of 7,863 patients from the LIPID (Long-Term Intervention with pravastatin in Ischemic Disease) study were included and had baseline and 1-year troponin levels measured. Median follow-up was 6 years. Baseline TnI tertiles were $<0.006$, $\geq 0.006$ to 0.018, and $\geq 0.018$ mg/ml. TnI increased in 23%, was unchanged in 51.3%, and decreased in 25.7% of patients. Despite adjustment for 23 risk factors and treatment, baseline levels of TnI were related to CHD deaths and MI (hazard ratio [HR]: 1.64). An increase in TnI was associated with increased CHD deaths and MI (HR: 1.31), and a decrease in TnI was associated with a decreased risk (HR: 0.9). Pravastatin decreased TnI levels by 0.003 ng/ml. The study concludes that baseline TnI levels and change at 1 year are independent predictors of CHD death and MI. Troponin levels are strong predictors of risk, and change modifies risk.

*Editorial Comment: Torbjørn Omland, p. 355*

CARDIAC GENETICS/GENOMICS

## *CYB561* Gene and Heart Rate 358

*Kuixing Zhang, Dekker C. Deacon, Fangwen Rao, Andrew J. Schork, Maple M. Fung, Jill Waalen, Nicholas J. Schork, Caroline M. Nievergelt, Neil C. Chi, Daniel T. O'Connor*

Zhang and colleagues attempt to understand the role of hereditary in the control of heart rate (HR), focusing on cytochrome b561 (*CYB561*), by using a twin pair design at rest and during environmental (cold) stress. Heritability was demonstrated for both basal/resting HR and stress-augmented HR, and the 2 HRs shared genetic determination. *CYB561* displayed 1 common genetic variant in the transcript region: A+1485G (rs3087776) in the 3′ (downstream of the open reading frame) untranslated region (UTR) (of the human CYB561 messenger ribonucleic acid [RNA]). In a twin/sibling sample, G+1485A influenced HR, with the minor (A) allele displaying a recessive effect. The effect of G+1485A on HR was extended by meta-analysis into 2 additional population samples, and the influence remained directionally consistent and significant. G+1485A disrupted a microRNA (hsa-miR-1294) recognition motif in the 3′-UTR (with A>G allele matches). The authors conclude that HR is a substantially heritable trait, with genetic influence by variation in the adrenergic pathway, here shown for mRNA translational control at the *CYB561* step of the transmitter formation.

*(continued on page A-30)*

NEWS FROM THE NHLBI

**Assessing Childhood Obesity** 369

*Charlotte A. Pratt, Sonia Arteaga, Catherine Loria*

In the past 30 years, the prevalence of obesity has more than doubled in children and tripled in adolescents; more than 12 million (17%) U.S. children and adolescents are now obese. Obese youth have a higher prevalence of vascular abnormalities, including left ventricular hypertrophy and atherosclerosis, but also hypertension, dyslipidemia, and type 2 diabetes, than normal-weight youth. There is a concern that obese children and adolescents will have a higher incidence of heart disease as adults. In this paper, Pratt and colleagues describes the ongoing National Heart, Lung and Blood Institute–initiated childhood obesity research. Strategies for improving clinical care of obese children and adolescents are also discussed.